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硕 士 学 位 论 文

三株TNF-α拮抗活性菌株的次级代谢产物研究

Studies on the Secondary Metabolites of three Strains with TNF-α Inhibitory Activity

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摘 要

肿瘤坏死因子-α（TNF-α）是巨噬细胞或单核细胞活化产生的一种细胞因子，在炎症反应、肿瘤免疫、细胞死亡、细胞增殖分化等多种生理和病理过程中发挥重要作用。适量的TNF-α介导的免疫反应对机体具有保护作用，但过量表达的TNF-α与其炎症因子一起作用是导致多种病理损伤，如自身免疫性疾病，感染性疾病等的原因[ ]，所以寻找小分子TNF-α抑制剂，阻断其过量产生或下游信号通路的传递，具有非常重要的临床意义。

寻找具有生物活性的新天然产物是发现新药先导化合物的主要途径，许多临床常用的药物均来自微生物次级代谢产物。而来自深海、极地、盐湖等极端环境中的菌株资源及植物内生真菌资源能够产生种类繁多、结构新颖、活性多样的次级代谢产物，是获得新结构和新活性天然产物的重要来源。

本论文对两株分离自特殊生境的有TNF-α拮抗活性的真菌及一株放线菌的次级代谢产物进行了研究，共分离鉴定了32个化合物，其中5个为新化合物。

从海藻内生真菌Aspergillus sp. AF044固体培养基发酵提取物中分离鉴定了13个化合物，包括7个生物碱类化合物（af7，af-8-8′，af1023，af1013，af1024，af-8-8，af1210a），4个苯甲酸类衍生物（af1，af8，af-91，af1023a），2个内酯类化合物（af23e，af422c3），其中af7、af1024和af1210a为新化合物。

从海洋小单孢菌Micromonospora sp. FXY256固体培养基发酵提取物中分离鉴定了4个化合物，包括2个呋喃酮类化合物（XY-1-3-1，F-4-4′），1个内酰胺类（XY-3），1个苯丙烯酸（XY-2）。

从喜树内生真菌Botryosphaeria sp. NXG-06固体培养基发酵提取物中分离鉴定了15个化合物，包括1个呋喃酮类化合物（M-1-6-10），5个倍半萜类化合物（M4-1-2，M5-4-1a，M5-4-1c，M5-4-1f，af11），2个酮类化合物（M5-4-1d，N-2-7），2个二倍半萜类化合物（M6′-1，N8），4个环二肽类化合物（N-2-1，N-2-6b，A-3a-1，A-1-2c-3），1个环烃类化合物（m12-1），其中af11和m12-1为新化合物。

对上述化合物在L929细胞模型上进行拮抗TNF-α活性筛选，结果显示化合物N-2-1具有一定拮抗活性。

本论文的研究结果表明：海洋微生物蕴藏着丰富的次级代谢产物资源，能够产生结构新颖、具有潜在生物活性的化合物；从天然产物中寻找TNF-α的小分子抑制剂是可行的。

关键词：次级代谢产物；TNF-α；真菌；放线菌

Abstract

Tumor necrosis factor-α¬(TNF-α) is a proinflammatory cytokine produced by macrophages and neutrophils , it plays an important role in diverse cellular events such as inflammation, tumorigenesis, cell death and differentiation. Appropriate amount of TNF-α-mediates protective immune reaction for the host, but overpressed of TNF-α is involved in systemic inflammation and many other acute phase reactions, so blocking the effect of TNF-α has been proved efficient for treating these diseases.

Bioactive natural products are main resource for discovering new drugs. Many important clinical medicines are microbial secondary metabolites. Microorganisms isolated from special living environment, such as deep-sea, polar region, saline and endophytic fungi, et al, can produce numerous metabolites with novel and varied skeletons or with unique bioactivities. In this study, the secondary metabolites of two fungi and one actinomycete with anti- TNF-α activity were investigated. Thirty- two compounds were isolated and elucidated from these three strains, including five new compounds.

The secondary metabolites of the strain spergillus sp. AF044 with agar medium solid were studied. Thirteen compounds were isolated, including seven alkaloids(af7,af-8-8′,af1023,af1013,af1024,af-8-8,af1210a), four formic acids (af1,af8,af-91,af1023a)and two lactones (af23e,af422c3), three new compounds (af7,af1024,af1210a) were obtained.

The secondary metabolites of the strain Micromonospora sp. FXY256A with agar medium solid were studied.Four compounds were isolated, including two Furan ketones(XY-1-3-1,F-4-4′), one lactam(XY-3), one cinnamic acid(XY-2).

The secondary metabolites of the strain Botryosphaeria sp. NXG-06 with agar medium solid were studied. Fifteen compounds were isolated, including one furan ketone(M1-6-10), five terpenoids(M4-1-2,M5-4-1a,M5-4-1c,M5-4-1f,af11),

two ketones(M5-4-1d,N-2-7), two diketopiperazines(M6′-1,N8), four cyclic dipeptides (N-2-1,N-2-6b,A-3a-1,A-1-2c-3) and one hydrocarbon(m12-1). af11 and m12-1 were new ones.

Compound N-2-1 exhibited moderate TNF-αinhibitory activity in L929 cells pretreatment with TNF-α

Our results indicated that marine actinomycetes an specific habitats fungi can produce novel metabolites. Exploring small-molecule inhibitors from the secondary metabolites of microorganisms is feasible.

Keywords: Secondary metabolites; TNF-α; Fungi; Actinomycetes

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